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Signed

Dated 6 November 2003

GB 0218153.5

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:

PROTEXEON LIMITED,
Aldwych House,
81 Aldwych,
LONDON,
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United Kingdom

Incorporated in the United Kingdom,

[ADP No. 08375784001]

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1/77

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P01/7700 0.00-0218153.5

Request for grant of a patent

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1. Your reference

P013875GB NJN

2. Patent application number
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0218153.5 05 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

~~I.C. Innovations Limited~~
~~47 Prince's Gate~~
~~Exhibition Road~~
~~London, SW1 2QA~~

IMPERIAL COLLEGE INNOVATIONS LIMITED
SHERFIELD BUILDING
LONDON
SW7 2AZ

Patents ADP number *(if you know it)*
861903300 1

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

AN ANALGESIC AGENT FOR NEWBORN OR FETAL SUBJECTS

5. Name of your agent *(if you have one)*

D Young & Co

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

21 New Fetter Lane
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EC4A 1DA

Patents ADP number *(if you know it)*

59006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
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b) there is an inventor who is not named as an applicant, or
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Yes

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Continuation sheets of this form	0
Description	11
Claim *(s)*	2
Abstract	1
Drawing *(s)*	2 + 2

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature D Young & Co. Date 05 August 2002

D Young & Co (Agents for the Applicants)

12. Name and daytime telephone number of person to contact in the United Kingdom — Neil Nachshen — 020 7353 4343

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AN ANALGESIC AGENT FOR NEWBORN OR FETAL SUBJECTS

The present invention relates to the field of analgesia. More specifically, the invention relates to an analgesic agent suitable for use in newborn and/or fetal subjects.

BACKGROUND

The human fetus and newborn are known to experience pain sensation [Anand KJS, Hickey PR. New Engl J Med 1987; 317:1321-1329]. However, of greater concern is that untreated pain in the newborn may adversely affect development of the central nervous system resulting in long-term physiological and psychological consequences [Taddio A, Katz J *et al*, Lancet 1997; 349:599-603; Graham YP, Heim C *et al*, Dev Psychopath 1999; 11:545-565; Anand KJS, Scalzo FM. Biol Neonate 2000; 77:69-82; Ruda MA, Ling Q-D *et al*, Science 2000; 289:628-630]. As a consequence, appropriate analgesic therapy is even more important in the anaesthetic management of the very young than in adults.

Nitrous oxide (N_2O) has been used for clinical anaesthesia in the young and the old for more than 150 years and remains the most commonly used anaesthetic gas. N_2O usage in the paediatric surgical patient is based upon the assumption that its anaesthetic and analgesic efficacy matches that seen in adults [Eger EI, Nitrous Oxide/N_2O. Elsevier, New York, 1985]. However, experiments have shown that N_2O lacks antinociceptive effects against thermal [Fujinaga M, Doone R, *et al*, Anesth Analg 2000; 91:6-10] and inflammatory [Ohashi Y, Stowell JM, *et al*, Pain 2002; in press] stimulation in rats under 3 weeks of age. If extrapolatable to humans, this would mean that N_2O is ineffective as an analgesic agent in subjects up to and including the toddler stage. A similar rationale was thought to apply to the use of xenon as an analgesic agent.

The present invention seeks to provide an analgesic agent capable of providing effective pain relief in newborn and/or fetal subjects which alleviates one or more of the above-mentioned problems.

STATEMENT OF INVENTION

In a first aspect, the present invention relates to the use of xenon in the preparation of a medicament for providing analgesia in a newborn subject and/or a fetal subject.

In a second aspect, the invention relates to a method of providing analgesia in a newborn subject, the method comprising administering to the subject a therapeutically effective amount of xenon.

In a third aspect, the invention relates to a method of providing analgesia in a fetal subject, the method comprising administering to the mother of the fetal subject a therapeutically effective amount of xenon.

DETAILED DESCRIPTION

As mentioned above, in a broad aspect, the present invention relates to the use of xenon as an analgesic agent in newborn and/or fetal subjects.

More specifically, the invention relates to the use of xenon in the preparation of a medicament for providing analgesia in a newborn subject.

Surprisingly, it has been found that xenon is capable of providing effective analgesia in the newborn, despite prior art indications to the contrary. Indeed, it is to be noted that the prior art has neither disclosed nor suggested the use of xenon as an analgesic agent in neonatal subjects.

In a preferred embodiment, the newborn subject is a mammal in the first four weeks after birth.

Even more preferably, the newborn subject is a human.

The present invention also relates to the use of xenon in the preparation of a medicament for providing analgesia in a fetal subject. In this embodiment of the invention, the xenon is preferably administered to the mother prior to or during labour.

During birthing, the fetus is subjected to mechanical stress which results in the activation of pain pathways. The present invention demonstrates that the impact of the activation of pain processing pathways in fetal subjects can be mitigated by the administration of xenon.

It is notable that to date, there has been no teaching or suggestion in the prior art to indicate that xenon could be used to provide analgesia in fetal subjects.

The advantage of using an inert, volatile gas such as xenon as an analgesic agent is that the molecule can be rapidly eliminated via respiration.

Xenon is a chemically inert gas whose anaesthetic properties have been known for over 50 years (Lawrence JH *et al*, J. Physiol. 1946; 105:197-204). Since its first use in surgery (Cullen SC *et al*, Science 1951; 113:580-582), a number of research groups have shown it has an excellent pharmacological profile, including the absence of metabolic by-products, profound analgesia, rapid onset and recovery, and minimal effects on the cardiovascular system (Lachmann B *et al*, Lancet 1990; 335:1413-1415; Kennedy RR *et al*, Anaesth. Intens. Care 1992; 20:66-70; Luttropp HH *et al*, Acta Anaesthesiol. Scand. 1994; 38:121-125; Goto T *et al*, Anesthesiology 1997; 86:1273-1278; Marx T *et al*, Br. J. Anaesth. 1997; 78:326-327). It has recently been discovered that xenon (which rapidly equilibrates with the brain) is an NMDA antagonist (Franks NP *et al*, Nature 1998; 396:324). Mechanistic studies on cultured hippocampal neurons have shown that 80% xenon, which will maintain surgical anaesthesia, reduces NMDA-activated currents by up to 60%. This powerful inhibition of the NMDA receptor

explains some of the important features of the pharmacological profile and is likely to be instrumental in the anaesthetic and analgesic effects of this inert gas.

The use of xenon in a pharmaceutical application is described in WO 00/76545, while the use of xenon as a neuroprotectant is described in WO 01/08692, the contents of which are incorporated herein by reference. Neither patent application discloses the possibility of xenon being an effective analgesic for newborn or fetal subjects.

In another preferred embodiment, the xenon is used in combination with one or more other pharmaceutically active agents. The agent may be any suitable pharmaceutically active agent including anaesthetic or sedative agents which promote GABAergic activity. Examples of such GABAergic agents include isoflurane, propofol and benzodiazapines.

The xenon may also be used in combination with one or more other analgesic agents. Suitable analgesic agents may include alpha-2 adrenergic agonists, opiates or non-steroidal antiinflammatory drugs. Examples of suitable alpha-2 adrenergic agonists include clonidine, detomidine, medetomidine, dexmedetomidine, brimonidine, tizanidine, mivazerol, guanabenz, guanfacine or dexmedetomidine.

The medicament of the present invention may also comprise other active ingredients such as L-type calcium channel blockers, N-type calcium channel blockers, substance P antagonists, sodium channel blockers, purinergic receptor blockers, or combinations thereof.

In one highly preferred embodiment of the invention, the xenon is administered by inhalation. More preferably, the xenon is administered by inhalation of a 20-70% v/v xenon/air mixture.

In another preferred embodiment, the medicament is in liquid form. For parenteral administration, the medicament may be used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood.

In a more preferred embodiment, the xenon is used in combination with a pharmaceutically acceptable carrier, diluent or excipient.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985).

The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol and the like. Examples of suitable diluents include ethanol, glycerol and water.

The medicament may comprise as, or in addition to, the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s). Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the "Handbook of Pharmaceutical Excipients, 2nd Edition, (1994), Edited by A Wade and PJ Weller.

Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

Up to now, a significant problem which has impeded the use of xenon as a new anaesthetic is its high cost and the need to use complex apparatus to minimise the volume used (low-flow systems), along with the need to scavenge the gas for reuse. A further problem is that the potency of xenon is relatively low. As a consequence, it had been suggested that volatile general anaesthetics may be solubilised in a lipid emulsion and administered intravenously (Eger RP *et al*, Can. J. Anaesth. 1995; 42:173-176). It is known in the art that local anaesthesia can be induced by intradermally injecting microdroplets of a general anaesthetic in a liquid form (Haynes DH, U.S. Patent Nos. 4,725,442 and 44,622,219). Typically these microdroplets are coated with a unimolecular phospholipid layer and remain stable in physiologically-compatible solutions. A similar approach is described in a recent patent application which proposes that xenon might be administered in this fashion (Georgieff M, European Patent Application No. 864329-A1).

Thus, in an even more preferred embodiment, the medicament is in the form of a lipid emulsion. By way of example, an intravenous formulation typically contains a lipid emulsion (such as the commercially available Intralipid®10, Intralipid®20, Intrafat®, Lipofundin®S or Liposyn® emulsions, or one specially formulated to maximise solubility) to sufficiently increase the solubility of the gas or volatile anaesthetic to achieve the desired clinical effect. Further information on lipid emulsions of this sort may be found in G. Kleinberger and H. Pamperl, Infusionstherapie, 108-117 (1983) 3.

The lipid phase of the present invention which dissolves or disperses the gas is typically formed from saturated and unsaturated long and medium chain fatty acid esters containing 8 to 30 carbon atoms. These lipids form liposomes in aqueous solution. Examples include fish oil, and plant oils such as soya bean oil, thistle oil or cottonseed oil. The lipid emulsions of the invention are typically oil-in-water emulsions wherein the proportion of fat in the emulsion is conventionally 5 to 30% by weight, and

preferably 10 to 20% by weight. Oil-in-water emulsions of this sort are often prepared in the presence of an emulsifying agent such as a soya phosphatide.

The lipids which form the liposomes of the present invention may be natural or synthetic and include cholesterol, glycolipids, sphingomyelin, glucolipids, glycosphingolipids, phosphatidylcholine, phosphatidylethanolamine, phosphatidyl-serine, phosphatidyglycerol, phosphatidylinositol.

The lipid emulsions of the present invention may also comprise additional components. These may include antioxidants, additives which make the osmolarity of the aqueous phase surrounding the lipid phase isotonic with the blood, or polymers which modify the surface of the liposomes.

It has been established that appreciable amounts of xenon maybe added to a lipid emulsion. Even by the simplest means, at 20°C and normal pressure, xenon can be dissolved or dispersed in concentrations of 0.2 to 10 ml or more per ml of emulsion. The concentration of dissolved gas is dependent on a number of factors, including temperature, pressure and the concentration of lipid.

The lipid emulsions of the present invention may be loaded with a gaseous or volatile anaesthetic. In general, a device is filled with the emulsion and anaesthetics as gases or vapours passed through sintered glass bubblers immersed in the emulsion. The emulsion is allowed to equilibrate with the anaesthetic gas or vapour at a chosen partial pressure. When stored in gas tight containers, these lipid emulsions show sufficient stability for the anaesthetic not to be released as a gas over conventional storage periods.

The lipid emulsions of the present invention may be loaded so that the xenon is at the saturation level. Alternatively, the xenon may be present in lower concentrations,

provided, for example, that the administration of the emulsion produces the desired pharmaceutical activity.

In one preferred embodiment, the medicament is in a form suitable for delivery intravenously (either by bolus administration or infusion), neuraxially (either subdural or subarachnoid) or transdermally.

The medicament of the present invention may also be administered in the form of an ointment or cream (lipid emulsion or liposomes) applied transdermally. For example, the medicament of the present invention may be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. Alternatively, the medicament of the present invention may be incorporated, at a concentration of between 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required. These ointments or creams are suitable for the local alleviation of pain and may be applied directly to damaged tissue, often with the aid of an optionally air-tight wound closure.

The concentrations employed in the medicament formulation may be the minimum concentration required to achieve the desired clinical effect. It is usual for a physician to determine the actual dosage that will be most suitable for an individual patient, and this dose will vary with the age, weight and response of the particular patient. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The medicament of the present invention may be for human administration or animal administration.

Thus, the medicament of the present invention may also be used as an animal medicament. In this regard, the invention further relates to the use of xenon in the preparation of a veterinary medicament for providing analgesia in newborn animals.

Preferably, the medicament of the present invention further comprises a veterinarily acceptable diluent, excipient or carrier.

For veterinary use, the medicament of the present invention, or a veterinarily acceptable formulation thereof, is typically administered in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

A further aspect of the invention relates to a method of providing analgesia in a newborn subject, the method comprising administering to the subject a therapeutically effective amount of xenon.

Yet another aspect of the invention relates to a method of providing analgesia in a fetal subject, the method comprising administering to the mother of the fetal subject a therapeutically effective amount of xenon.

In a preferred embodiment, the xenon is administered to the mother prior to or during labour. Preferably, the xenon alleviates the pain associated with the mechanical stress experienced by the fetus during labour.

Advantageously, administering xenon to the fetus via the mother has the concomitant benefit of alleviating labour pain experienced by the mother during delivery. Thus, the administration of xenon to the mother prior to or during labour has the dual effect of providing pain relief to both the fetus and the mother.

The present invention is further described by way of the following non-limiting examples and with reference to Figures 1 and 2, wherein:

Figure 1 shows cross sections of the spinal cord at the lumbar level stained for c-Fos in 7 day-old Fischer rats after receiving formalin. Figure 1A shows a section treated with air/formalin, whereas Figure 1B shows a section treated with xenon/formalin.

Figure 2 shows cross sections of the spinal cord at the lumbar level stained for c-Fos in 7 day-old Fischer rats after receiving formalin. Figure 2A shows a section treated with air/formalin, whereas Figure 2B shows a section treated with N_2O/formalin.

EXAMPLES

The analgesic efficacy of xenon was investigated in a neonatal rat pup. A 7 day neonatal rat pup is known to be developmentally equivalent to a human full term fetus with respect to pain processing pathways.

A 7 day old rat was injected with formalin into the hindpaw during exposure to either air or xenon (70%v/v). 90 minutes later the animal was killed and the spinal cord removed; evidence of activation of pain-processing pathways by formalin was sought by counting he number of cFos positive neurones in the dorsal horn of the spinal cord.

In Figure 1, xenon almost completely attenuated formalin-induced c-Fos positive neurones (air). By comparison a normally analgesic dose of nitrous oxide in the adult rat did not change formalin-induced c-Fos positive neurones (Figure 2).

From the results, it can be concluded that xenon interrupts pain processing so that pain signals will not travel to the brain and hence pain, as well as the long-term consequences of untreated pain, is mitigated in the neonatal population.

Various modifications and variations of the described methods of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific

preferred embodiments, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry or related fields are intended to be within the scope of the following claims.

CLAIMS

1. Use of xenon in the preparation of a medicament for providing analgesia in a newborn subject and/or a fetal subject.

2. Use according to claim 1 wherein the newborn subject is a mammal in the first four weeks after birth.

3. Use according to claim 1 or claim 2 wherein the newborn or fetal subject is a human.

4. Use according to any preceding claim wherein the xenon is used in combination with a pharmaceutically acceptable carrier, diluent or excipient.

5. Use according to any preceding claim wherein the xenon is administered in combination with a sedative, an anaesthetic agent or a further analgesic agent.

6. Use according to any preceding claim wherein the medicament is in gaseous form.

7. Use according to claim 6 wherein the medicament is in the form of a 20 to 70% v/v xenon/air mixture.

8. Use according to any one of claims 1 to 5 wherein the medicament is in liquid form.

9. Use according to claim 8 wherein the medicament is in the form of a lipid emulsion.

10. Use according to claim 8 or claim 9 wherein the medicament is in a form suitable for intravenous, neuraxial or transdermal delivery.

11. A method of providing analgesia in a newborn subject, the method comprising administering to the subject a therapeutically effective amount of xenon.

12. A method of providing analgesia in a fetal subject, the method comprising administering to the mother of the fetal subject a therapeutically effective amount of xenon.

13. A method according to claim 11 or claim 12 wherein the xenon is administered in combination with a pharmaceutically acceptable carrier, diluent or excipient.

14. A method according to any one of claims 11 to 13 wherein the xenon is administered in the form of a 20 to 70 % v/v xenon/air mixture.

15. A method according to any one of claims 11 to 13 wherein the xenon is administered in the form of a lipid emulsion.

16. A method according to any one of claims 11 to 13 or 15 wherein the xenon is administered intravenously, neuraxially or transdermally.

ABSTRACT

AN ANALGESIC AGENT FOR NEWBORN OR FETAL SUBJECTS

In a first aspect, the present invention relates to the use of xenon in the preparation of a medicament for providing analgesia in a newborn subject and/or a fetal subject.

In a second aspect, the invention relates to a method of providing analgesia in a newborn subject, the method comprising administering to the subject a therapeutically effective amount of xenon.

In a third aspect, the invention relates to a method of providing analgesia in a fetal subject, the method comprising administering to the mother of the fetal subject a therapeutically effective amount of xenon.

FIGURE 1

(A)

(B)

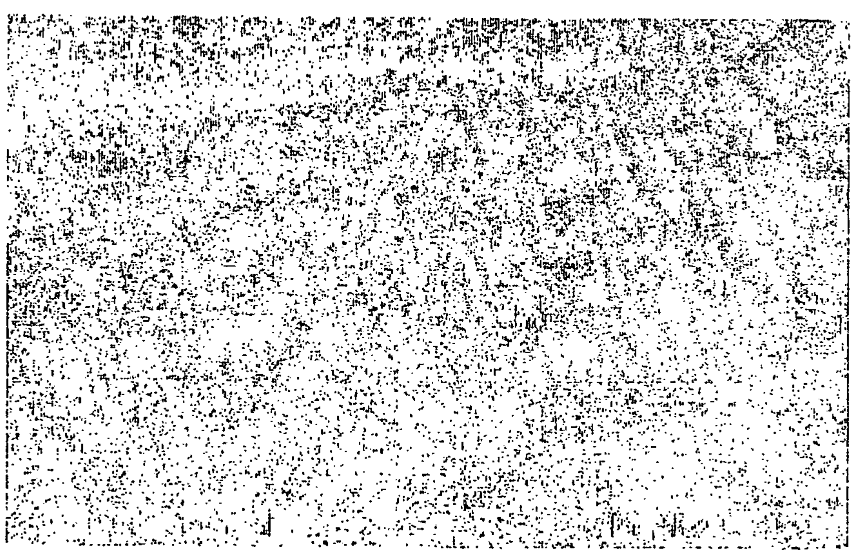
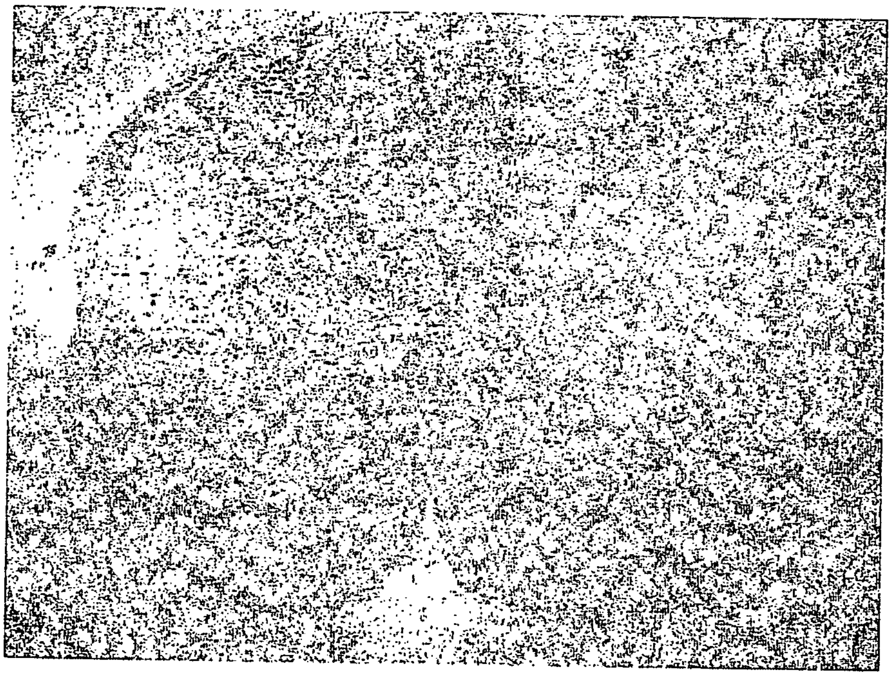


FIGURE 2

(A)



(B)